REMARKS/ARGUMENTS

The Pending Claims

Claims 5, 8, 10-12, 18, 20, and 32-35 are pending and are directed to a method of enhancing an immune response in a subject (claims 5, 8, 10-12, 32, and 34) and a method of treating a subject with a condition comprising a deficiency of at least one of memory B cells and plasma cells (claims 18, 20, 33, and 35).

Amendments to the Claims

Claims 5, 18, and 32-35 have been amended to clarify the claimed subject matter. In particular, claims 5 and 18 have been amended to clarify that the composition comprises (i) the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or (ii) a variant of the amino acid SEQ ID NO: 1, wherein the variant comprises the amino acid sequence of SEQ ID NO: 1 except for 1-5 amino acid substitutions, deletions, or additions, and wherein the variant retains the ability to bind to the IL-21 receptor and produce a physiological effect produced by binding of the IL-21 polypeptide to the IL-21 receptor. Claims 5 and 18 also have been amended to clarify that the composition (comprising the (i) IL-21 polypeptide or (ii) variant thereof) induces differentiation of at least one B cell into one or more of a memory B cell and a plasma cell.

Claims 32 and 33 have been amended to recite that the composition comprises (i) the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1. Claims 34 and 35 have been amended to recite that the composition comprises (ii) the variant of the amino acid sequence of SEQ ID NO: 1, wherein 1-5 amino acids of SEQ ID NO: 1 have been substituted, deleted, or added.

Claims 32 and 34 also have been amended to depend from claim 5.

No new matter has been added by way of these amendments to the claims.

Summary of the Office Action

The Office rejects claims 5, 8, 10-12, 18, 20, and 32-35 under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description, and for allegedly lacking enablement.

The Office objects to claims 32-35 for allegedly being in improperly dependent form for failing to further limit the subject matter of a previous claim.

The Office rejects claims 32 and 34 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Reconsideration of these objections and rejections is hereby requested.

Discussion of the Written Description Rejection

The written description rejections are traversed for the following reasons.

A. IL-21 Polpeptide Variants Are Adequately Defined by the Specification

The Office contends that the claims encompass unspecified variants of polypeptides of any undetermined length which can be fragments with or without the claimed functionality (see page 4 of the Office Action). This rejection is traversed for the following reasons.

The pending claims, as amended, recite a composition comprising (i) an IL-21 polypeptide comprising SEQ ID NO: 1 or (ii) a variant of the IL-21 polypeptide that comprises SEQ ID NO: 1 except for 1-5 amino acid substitutions, deletions, or additions. The claims require that the defined variant retains the ability to bind to the IL-21 receptor and produce the same physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor. Furthermore, the claims require that the composition (comprising the (i) IL-21 polypeptide or (ii) defined variant thereof) induces differentiation of at least one B cell into one or more of a memory B cell and a plasma cell.

Accordingly, the pending claims recite that the variant has at most 5 mutations of SEQ ID NO: 1. The amino acid sequence of SEQ ID NO: 1 contains 160 amino acids. Thus, the variant has more than 96.8% identity to SEQ ID NO: 1 and must produce the same

physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor. Furthermore, the defined variant (as part of a composition defined in the claims) must induce differentiation of at least one B cell into one or more of a memory B cell and a plasma cell. Assays to determine if an IL-21 variant produces the above-described effects (e.g., real-time PCR) are known in the art and are described in the specification at, for instance, page 41, line 19, through page 44, line 16; and Examples 3-5.

Thus, the claims define a variant of a particular sequence (i.e., SEQ ID NO: 1 with at most 5 mutations) with a particular function. The specification describes variants for use in the invention at, for example, page 31, lines 1-26. In particular, the specification cites to U.S. Patent Application Publication 2003/0003545 (Ebner et al.) for the disclosure of variants that differ from IL-21, but retain the essential properties thereof. Ebner et al. discloses conserved regions of IL-21 polypeptide in Figures 1, 4, 6A-B, and 7, and Tables I-III, and regions of identity between IL-21 and other interleukins in Figures 3A-C. One of ordinary skill in the art would recognize that conserved regions may be involved in protein function and, therefore, should not be mutated in the IL-21 polypeptide variant.

Additionally, at the effective filing date of the application, one of ordinary skill in the art was aware that cytokines, such as IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, share common structures. Given the similarities between cytokines, one of ordinary skill in the art would recognize that conserved regions, such as the helices of IL-21 that correspond to the helices of IL-4 (which helices are known to interact with the IL-4 receptor), should not be mutated in order to maintain function. One of ordinary skill in the art easily could determine the helices of IL-21 by molecular modeling based on the structure of other cytokines, such as IL-4 (see, e.g., Hage et al., *Cell, 97*: 271-281 (1999); copy submitted herewith).

The Office contends that the assays described in the specification to determine suitable variants merely are an invitation for one of ordinary skill in the art to try to follow the disclosed instructions to make and use the claimed invention. Applicants note that one of ordinary skill in the art would have been able to use routine known methods (e.g., real-time PCR) to determine whether a variant retained the physiological functions of the IL-21 polypeptide of SEQ ID NO: 1 (e.g., activation of the JAK/STAT signaling pathway,

induction of differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells, induction of expression of mRNA for Blimp-1 and Bcl-6, and inhibition of expression of Pax5 mRNA) and the ability to induce differentiation of at least one B cell into one or more of a memory B cell and a plasma cell.

Accordingly, the level of experimentation required to determine if a variant met the required structural and functional requirements would be minimal and certainly not "undue."

B. Comparison of Description of IL-21 Polypeptide Variants to the Examples in the Revised Interim Written Description Guidelines Training Materials

Applicants note that Example 14 of the "Revised Interim Written Description Guidelines Training Materials" downloaded from the U.S. Patent and Trademark Office website (www.uspto.gov/web/offices/pac/writtendesc.pdf) describes a situation wherein a claim is directed to a protein of a particular sequence (SEQ ID NO: 3) or variants thereof that (i) are at least 95% identical to SEQ ID NO: 3 and (ii) perform a particular function. According to the example, a single species is disclosed (i.e., SEQ ID NO: 3). According to the training materials, the single species is representative of the genus because all members of the genus have at least 95% structural identity with SEQ ID NO: 3 and because of the description of an assay for identifying all of the at least 95% identical variants of SEQ ID NO: 3 with the claimed functional activity. Therefore, the training materials conclude that the Applicants were in possession of the necessary common attributes possessed by the members of the genus, such that the disclosure is determined to meet the written description requirements.

The situation described in Example 14 of the training materials is similar to that in the present application, wherein the variant is defined by (i) greater than *96%* identity to a particular sequence (SEQ ID NO: 1) and (ii) the ability to bind to the IL-21 receptor and produce a physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor and induce differentiation of at least one of the mature B cell and the B cell progenitor into one or more of a memory B cell and a plasma cell. As discussed above, based on the teachings in the specification and using routine methods, one of ordinary skill in the art could determine whether the defined variant has the claimed functional activity. Accordingly, based on the situation described in the

training materials in Example 14, the IL-21 polypeptide variant of the pending claims would be considered to meet the written description requirements.

For the above-described reasons, based on the teachings in the specification and what was known in the art at the time the application was filed regarding the conserved regions of IL-21 polypeptide, one of ordinary skill in the art would have recognized that Applicants had possession of an IL-21 polypeptide variant comprising SEQ ID NO: 1 except for 5 or less defined modifications for use in the inventive methods. For these reasons, Applicants request that the written description be withdrawn.

Discussion of the Enablement Rejections

The enablement rejections are traversed for the following reasons.

A. Defined IL-21 Polpeptide Variants are Enabled by the Specification

The Office contends that the claims are not enabled for the genus of IL-21 polypeptide variants. As discussed above, the claims define a variant of a particular sequence (i.e., SEQ ID NO: 1 with at most 5 defined modifications) with a particular function. Conserved regions of the IL-21 polypeptide are known in the art, such that one of ordinary skill in the art would recognize areas where mutations should not occur in order to maintain the functionality. As discussed above, based on the teachings in the specification and using routine methods, one of ordinary skill in the art could determine whether the defined variant has the claimed functional activity. For these reasons, one of ordinary skill in the art would understand how to make an IL-21 polypeptide variant that comprises SEQ ID NO: 1, except for 5 or less mutations of SEQ ID NO: 1, and use the variant in the inventive methods.

B. The Enhancement of an Immune Response Against Viral Antigens Is Enabled by the Specification

The Office also contends that the specification does not provide sufficient guidance for enhancing an immune response against any viral antigen by administering one or more of a memory B cell and plasma cell that are produced *ex vivo* to the subject.

The specification discloses that a population of cells (e.g., B cell progenitors) that have been isolated from a subject can be contacted with IL-21 polypeptide or variant thereof, which results in the differentiation of the B cells into plasma cells and/or memory cells, which are then isolated (*see*, e.g., page 34, line 18, through page 35, line 3; and Examples 3-5). Furthermore, the specification discloses the administration of the isolated memory B cells and plasma cells to the subject to enhance an immune response (*see*, e.g., page 34, line 18, through page 35, line 3). Antibody production (e.g., by plasma cells) is an essential element of the immune response, such that one of ordinary skill in the art would recognize that the inventive methods would be effective in enhancing an immune response in a subject.

As discussed in the previous Reply to Office Action, the use of antibodies to inhibit virus infection is a well-established technology. For example, Mascola et al. and Baba et al. reported the protection afforded by the introduction of neutralizing antibodies against HIV infection in the February 2000 issue of the journal *Nature Medicine* (see, Mascola et al., *Nature Medicine, 6(2)*: 207-210 (2000) and Baba et al, *Nature Medicine, 6(2):* 200-206 (2000)). Furthermore, Applicants cited to several post-filing references describing clinical trials using antibody therapy to enhance an immune reaction against viral infection. As additional evidence that one of ordinary skill in the art would have been aware of the success of antibody therapy at the effective filing date of the application, Glennie et al. (*Immunology Today, 21(8)*: 403-410 (2000); submitted herewith), which published in 2000 (i.e., before the effective filing date of the application), describes the clinical development of antibodies that enhance immune responses against viral infection, cancer, and autoimmune diseases (see, e.g., Table 1).

While T cell responses contribute to viral immunity, memory B cells and plasma cells produce the antibodies that provide the majority of immunity against many viral infections. In many cases, antibody immunity is necessary and sufficient for vaccine-induced immunity against viruses. Although it is commonly thought that the immune response to intracellular pathogens includes T cells, in practice, most antiviral vaccines work mainly by eliciting antibodies that bind and neutralize the virus. This is supported by epidemiology of natural infections, protection by immunoglobulin preparations, and experience with antiviral vaccines as discussed in further detail below.

1. Epidemiology of Natural Infections

For many viruses, such as poliovirus, epidemiological studies have shown that prior infection protects, but only when the challenge virus matches the serotype of the prior infection. Serotypes are defined by antibodies. Antibodies from a person infected with a virus of a particular serotype (e.g., polio serotype 1) kill all viruses of the same type, but they do not kill viruses of a different serotype. For example, once a person is infected with polio serotype 1, the person cannot be reinfected with the same serotype; however, the person still can be infected with the other two polio serotypes. The fact that antibody binding (serotypes) defines who is protected and who is not demonstrates that virtually all naturally acquired immunity against viral infections, such as polio infections, comes from antibodies (see, e.g., Paffenbarger et al., *Am. J. Hyg., 74*: 311-325 (1961); copy submitted herewith).

Similarly, influenza virus infects the same people year after year. To do this, the virus changes its serotype, through a process of mutation leading to antigenic drift. The mutations occur at discrete antibody binding sites (see, e.g., Wiley et al., *Nature, 289*: 373-378 (1981); copy submitted herewith). Antigenic drift in influenza, resulting in immune escape, demonstrates that antibodies provide the main defense against viral infections, such as influenza infection.

2. Protection by Immunoglobulin Preparations

Immunoglobulins alone can protect against viral infections. For example, injection of hyperimmune immunoglobulin against hepatitis B virus protects against infection. Beasley et al. (*Dev. Biol. Stand., 54*: 363-375 (1983); copy submitted herewith) demonstrates that babies born to highly infectious mothers had a 92% risk of infection without immune globulin, and this risk could be cut to 26% with gamma globulin injections at birth, 3 months, and 6 months. This effect was due entirely to transfer of antibody-mediated immunity. Even today (over 25 years later), the recommended treatment for these babies is hyperimmune globulin in one arm and recombinant hepatitis B vaccine in the other.

Other immunoglobulin preparations have been shown to protect against poliovirus (see, e.g., Hammon et al., *JAMA, 151*: 1272-1285 (1953); copy submitted herewith) and hepatitis A virus infection (Havens et al., *JAMA, 129*: 270-272 (1945); copy submitted

herewith). Once again, antibodies alone were sufficient to protect against these viral infections, and immunity waned at the same rate as the metabolism of these antibodies.

3. Antiviral Vaccines

A live viral vaccine, such as the Sabin polio vaccine, can elicit both T cell immunity and antibodies. In contrast, a killed viral vaccine or a non-infectious recombinant vaccine would elicit primarily antibodies and almost no cytolytic T cells. Yet, many successful vaccines are of the latter type, despite failure to elicit a T cell response. For example, Salk polio vaccine is primarily based on eliciting antibodies, not T cells. Similarly, recombinant hepatitis B vaccine and recombinant human papilloma virus (HPV) vaccine are both strong inducers of antibodies, but weak inducers of T cell immunity. Yet, the vaccines achieve protection in 99% of vaccinees.

As with natural infection, Salk polio vaccine only can protect against the serotype of which the vaccine is made. To protect against all circulating viruses, polio vaccine must contain all three serotypes. If immunity were not based on antibodies, these serotypes would not be so important. The requirement for covering all three serotypes indicates that antibodies convey immunity.

Similarly, recombinant HPV vaccine contains two L1 proteins that correspond to the two most prevalent serotypes (see, e.g., Kahn et al., *Lancet, 369*: 2135-2137 (2007); copy submitted herewith). The vaccine does not work against serotypes that are not included in the vaccine; however, the vaccine provides nearly complete immunity against serotypes 16 and 18, which together cause 70% of cervical cancers. Immunity depends on matching serotypes between the vaccine and the challenge HPV virus, which is determined by antibodies, not T cells. Accordingly, effective immunity depends on antibodies.

The influenza virus escapes from neutralizing antibodies by mutating at key antigenic sites. Careful study of these sites locates them on the 3-dimensional structure of influenza hemagglutinin protein where antibodies bind. The influenza vaccine must be reformulated each year so it matches the serotypes of the emergent strains. The differences in strains are defined by antibody reactivity, indicating that immune escape occurs where antibodies bind the virus.

For hepatitis B vaccine, the correlates of immunity were identified by Szmuness et al. (*Hepatology, 1*: 377-385 (1981); copy submitted herewith). All patients with antibody titers greater than 10 mIU/ml were protected from hepatitis B infection, while all of the infections occurred in patients with lower antibody titers. This correlation occurred because antibodies were the source of immunity to hepatitis B virus.

In sum, these three lines of evidence (i.e., epidemiology of natural infections, protection by immunoglobulin preparations, and experience with antiviral vaccines) indicate that B cells and plasma cells producing antibodies against a virus are a potent way to elicit protective immunity against the virus.

Thus, based on the description in the specification and what was known in the art at the effective filing date of the application, one of ordinary skill in the art would expect that the administration of one or more of a memory B cell and the plasma cell would enhance an immune response. Additionally, one of ordinary skill in the art would have recognized how to perform the inventive methods without undue experimentation and with an expectation of success. For these reasons, Applicants request that the enablement rejections be withdrawn.

Discussion of the Claim Objections

The Office contends that claims 32-35 fail to further limit the subject matter of claim 5 or 18. These objections are traversed for the following reasons.

Claims 5 and 18 recite that the population of cells is contacted with a composition comprising (i) an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or (ii) a variant of the amino acid SEQ ID NO: 1 with 1-5 amino acid substitutions, deletions, or additions.

Claims 32 and 34 recite that the composition comprises (i) the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1. Claims 33 and 35 recite that that the composition comprises (ii) the variant of the amino acid SEQ ID NO: 1 with 1-5 amino acid substitutions, deletions, or additions. Thus, claims 32-35 further define claims 5 and 18 by reciting the particular component of the composition (i.e., either (i) and (ii)).

In an effort to make claims 32-35 even more clear, Applicants have been amended the claims to recite "...(i) the IL-21 polypeptide..." in claims 32 and 34, and "...(ii) the variant...." in claims 33 and 35.

For the above-described reasons, Applicants request that claim objections be withdrawn.

Discussion of the Indefinite Rejections

The Office points out that claims 32 and 34 depend from a canceled claim. Claims 32 and 34 have been amended to depend from claim 5. Applicants believe that the claim objections are moot in view of the amendments to the claims.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

Jeremy M. Jay, Reg. No. 63,587
LEYDIG, VOIT & MAYER
700 Thirteenth Street, N.W., Suite 300
Washington, DC 20005-3960
(202) 737-6770 (telephone)
(202) 737-6776 (facsimile)

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